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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
07/20/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/553,078	STRATEN ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *June 8, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45 and 54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/23/06, 3/23/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1,2,4,7,12,14-16,18-21,24,27,30,32,33,35,37,39,41,45,47-49,51 and 53-59.
Continuation of Disposition of Claims: Claims withdrawn from consideration are 1,2,4,7,12,14-16,18-21,24,27,30,32-35,37,39,41,47-49,51 and 53.

DETAILED ACTION

1. Applicant's election without traverse of Group IV, claim 45, in the reply filed on June 8, 2007 is acknowledged.

2. Claims 1, 2, 4, 7, 12, 14-16, 18-21, 24, 27, 30, 32, 33, 35, 37, 39, 41, 47-49, 51, and 53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on June 8, 2007.

3. Claims 54-59 have been added.

Claims 45 and 54-59 are under examination.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on June 23, 2006 and March 23, 2007 have been fully considered by the examiner and an initialed copy of the IDS is included with the mailing of this office action.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor.
The citizenship is listed as a nationality (Danish) rather than a country (Denmark).

Specification

6. The abstract of the disclosure is objected to because it contains legal phraseology. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

7. The disclosure is objected to because of the following informalities: the specification contains typographical errors, for example, on page 26, line 10 “adoptes” should read “adopted” and on page 30 line 3 “emergency” should read “emergence”.

Additionally, the Greek symbols throughout the specification appear as boxes, for example on page 67 line 28.

Appropriate correction is required throughout.

8. The use of the trademarks Herceptin™, Quadramet™, and LymphoCide™ have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The trademark symbols and generic terminology have not been included for the trademarks in the specification.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 45 and 54-59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a.) Claims 45 and 54-59 are indefinite for reciting the phrases "a polypeptide fragment" "said fragment comprising a peptide" and "said polypeptide fragment comprises at the most 15 amino acids" in claim 45. It is not clear if the peptide and the

polypeptide are the same length fragments. The World Net online dictionary defines a polypeptide as "a peptide containing 10 to more than 100 amino acids" and a peptide as "amide combining the amino group of one amino acid with the carboxyl group of another". Absent a specific definition in applicant's specification of a peptide and a polypeptide, it has been interpreted for this office action that the polypeptide fragment and the peptide fragment are two different fragments.

b.) Claims 45 and 54-59 are indefinite for reciting the phrase "functional equivalents" in claim 45. It is not clear what the function of the peptide is.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 45 and 54-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

> They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a method for raising a specific T-cell response against an epitope of ML-IAP in an individual, comprising the steps of administering to the individual a polypeptide fragment capable of raising a specific T-cell response, said fragment comprising a peptide selected from the group consisting of rlqeertck (SEQ ID No. 245), rlqeertckv (SEQ ID No. 297), qlcpicrapv (SEQ ID No. 298), velppgardv (SEQ ID No. 301), and functional equivalents having at least 75% sequence identity thereto, wherein said polypeptide fragment comprises at the most 15 amino acids and raising a specific T-cell response against an epitope of ML-IAP in the individual.

The specification discloses detection of a CTL response against the peptides of SEQ ID Nos. 245, 297, 298, and 301 in peripheral blood cells from melanoma patients (examples 2 and 3). The specification does not disclose administering the peptides of SEQ ID Nos. 245, 297, 298 or 301 to individuals to induce a T cell response. The specification does not disclose the specific T-cell response to include T cell anergy, or inactivation. The specification does not disclose peptides having 75% sequence identity to SEQ ID Nos. 245, 297, 298 or 301.

The prior art teaches that tumor cells are phenotypically less stable than normal cells and can escape the immune response of the host by many mechanisms including deficient antigen processing by tumor cells, production of inhibitory substances such as cytokines, tolerance induction, rapidly growing cells which can overwhelm a slower

immune response, failure of the host to respond to an antigen due to immunosuppression, tumor burden, infections or age, deficient antigen presentation with the host and failure of the host effector cells to reach the tumor due to the stromal barrier (Paul, Fundamental Immunology, (text), 1993, page 1163, second column, first sentence under the heading "Factors Limiting Effective Tumor Immunity" and Table 4). The specification has provided evidence that two T-cell clones are able to lyse tumor cells expressing an epitope of the claimed tumor rejection antigen precursors in vitro (see example 5). Paul teaches that lymphocytes from tumor bearing patients have frequently been found to be cytotoxic to their own tumor cells in vitro, but that this effect was blocked by the addition of sera from said patients. Paul teaches that the constituent of the sera which caused the blocking of the cytotoxicity was unknown, but that antibodies, antibody-antigen complexes and shed antigen have all been implicated in the blocking phenomenon (Paul page 1167, second paragraph under the heading "Immunological Enhancement and Blocking Factors"). Paul also notes that in some cases, immune response to a tumor antigen may sometimes stimulate the growth of the tumor cells directly (last line under the heading "Immunological Enhancement and Blocking Factors", page 1167). With respect to the blocking factor found in serum, Apostolopoulos et al (Nature Medicine, 1998. vol. 4, pages 315-320) teach that endogenous antibodies present at the time of administration of a tumor peptide re-routes the immune response from a cellular response to a humoral response. In preclinical experiments with mice, MUC1 peptides targeted to the mannose receptor produce high levels of CTL and a low level of antibodies. However, in human clinical

trials a low level of CTL and a high level of humoral response was observed (Apostolopoulos, page 315, first column, bridging paragraph). Apostolopoulos et al teach that the presence of endogenous antibodies which bind to the MUC1 peptide was responsible for this re-routing of the immune response from cellular to humoral due to the Fc portion of the antibody (page 319, first column, lines 7-10). Apostolopoulos et al teach that mice are devoid of these antibodies (page 315, second column, lines 9-13) and are thus able to effectively mount a cellular immune response against the target antigen. Apostolopoulos et al teach that these findings have implication for other immunotherapy approaches (page 318, lines 4-8, under the heading "Discussion"). In support of these conclusions Jager et al (PNAS, 2000. Vol. 97, pages 12198-12203) teach that patients who do not have antibodies to the cancer testis antigen, NY-ESO-1, were able to generate a specific T-cell response to NY-ESO after intradermal administration, whereas patients having antibodies prior to treatment which reacted with said antigen already had T-cells which reacted with target cells expressing said antigen in vitro, and said positive patients did not develop significant CTL in response to the administered NY-ESO antigen. These references serve to demonstrate that the induction of an anti-tumor CTL response after the administration of a tumor peptide is unpredictable.

Paul (ibid) states that deficient antigen presentation is a mechanism by which tumor cells escape immune detection. This is corroborated by the observations set forth in the abstracts of Semino et al (Journal of Biological Regulators and Homeostatic Agents, 1993. Vol. 7, pages 99-105) and the abstract of Algarra et al (International

Journal of Clinical and Laboratory Research, 1997. Vol. 27, pages 95-102) which all teach that primary tumors in situ are often heterogeneous with respect to MHC presentation. The effect of the claimed vaccine upon such a heterogeneous tumor has not been demonstrated by the specification. More currently, the abstract of Bodey et al (Anticancer Research, 2000. Vol. 20, pages 2665-2676) teaches that the failure of methods of treating cancer comprising the administration of tumor antigens is due to the failure of cancer vaccines to eliminate the most dangerous cells within a tumor which are so de-differentiated that they no longer express cancer cell specific molecules.

Ohlen et al (Journal of Immunology, 2001. Vol.166, pages 2863-2870) teach that T-cells recognizing normal proteins expressed in tumors can be isolated in vitro, but that the existence of said T-cells does not preclude in vivo anergy induction and deletion (page 2863, second column, lines 1-6 of the last paragraph). Antoinia et al (International Immunology, 1995. Vol. 7, pages 715-725) teach that T-cells which are impaired in the ability to proliferate in response to antigen and unable to reject tumors in vivo were fully functional as CTL lymphocytes in vivo (page 724, first column, first full paragraph). Yu and Restifo (Journal of Clinical Investigation, 2002. Vol. 110, pages 289-294, especially page 292) teach that even when increased anti-tumor T-cell precursors have been induced by vaccination, the clinical response is partial and transient and most patients eventually succumb to progressively growing tumors. These references serve to demonstrate that the lysis of target cells expressing DAGE antigen in vitro does not constitute evidence that said T-lymphocytes would be effective at lysing tumor cells in vivo.

Regarding "functional equivalents" and other variants, the art teaches that "putative epitopes" can be predicted using a computer to scan the sequence of the gene (antigen) for amino acid sequences that contain a "motif" or a defined pattern of amino acid residues associated with a particular MHC (HLA) allele, but that upon testing in standard functional assays, the vast majority of these "predicted" epitopes failed to be immunogenic (Burch WO 03/084467 published October 16, 2003). Further, Ionnides et al (U.S. 6,514,942 issued February 4, 2003) teach that not all HLA-A2 anchor containing peptides are antigenic (column 10, lines 3-4). It is reasonable to construe that the "predicted epitopes" referred to by Burch and Ionnides et al failed to elicit a CTL immune response. Thus, there is no reliable nexus between a theoretical peptide immunogen designed to fit into a particular HLA molecule and the eliciting of an immune response thereby.

Regarding raising a "specific T-cell response", the specification only contemplates using the "activated" T cells to induce an anti-tumor response, while the phrase "specific T-cell response" includes induction of T cell anergy as well as induction of activated T cells. Roitt, et al. (Really Essential Medical Immunology, 2004. Blackwell Publishing, eBook. Pages 75-79) teach two signals are required to activate a T cell, an antigen in association with MHC class II on the surface of an antigen presenting cell (APC) is capable of providing one of the signals, the second signal can be between CD40 on the APC and CD40L on the T-cell. If a T cell receives only one signal it is rendered angeric or unresponsive to further stimulation by antigen (see figure 7.2 and "activation of T-cells requires two signals" pages 75-76). Thus, "specific T-cell

response" includes both activation and inactivation of T cells. As applied to the generation of "activated" T cells for the induction of an anti-tumor effect, Hoffman et al (International Journal of Cancer, 2005. vol. 115, pages 98-104) teach that although certain vaccination approaches with tumor-associated peptides or proteins can induce tumor-specific T cell responses in patients, the efficacy and response rate of such treatments is unsatisfactory and far from routine (page 98, first column, last paragraph).

Regarding peptides having at least 75% sequence identity, protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology, 1990. Vol 111, pages 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al, Molecular and Cellular Biology, 1988. Vol 8, No 3. pages 1247-1252). Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin (Schwartz et al, Proc Natl Acad Sci, 1987. Vol 84 pages 6408-6411). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase (Lin et al, Biochemistry, 1975. Vol 14 pages 1559-1563). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential

chemical modification, will often dramatically affect the biological activity of the protein. The results of the construction of synthetic proteins remain very unpredictable as Burgess et al, Lazar et al, Schwartz et al, and Lin et al conclusively demonstrate.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to raise a specific T-cell response against an epitope of ML-IAP in an individual by administering a peptide of SEQ ID Nos. 245, 297, 298 or 301. The specification does not teach how inoculating an individual with compositions comprising the peptides of SEQ ID Nos. 245, 297, 298 or 301 overcomes the back-and-forth struggle between host and tumor, a process which creates highly resistant, poorly immunogenic, and extremely aggressive clones of tumor cells.

In view of the lack of the predictability of the art to which the invention pertains undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inducing a specific T-cell response in an individual, commensurate in scope with the claimed invention.

13. Claims 45 and 54-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 75% identity with SEQ ID Nos. 245, 297, 298, or 301. While the amino acid sequence of SEQ ID Nos. 245, 297, 298, and 301 are adequately described in the specification as-filed, thereby providing an adequate basis for the polypeptides of SEQ ID Nos. 245, 297, 298, or 301; there is insufficient written description as to the identity of a polypeptide having at least 75-99% sequence identity to SEQ ID Nos. 245, 297, 298, or 301 that would still maintain the function of the polypeptide. Consequently, the specification does not provide an adequate written description of a polypeptide having at least 75% sequence identity to SEQ ID Nos. 245, 297, 298, or 301.

The specification as filed does not provide adequate written description support for a polypeptide having at least 75% sequence identity to SEQ ID Nos. 245, 297, 298 or 301. Polypeptides having diverse functions are encompassed by the phrase 75% identity. Thus a broad genus having potentially highly diverse functions is encompassed by the phrase 75% sequence identity and conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. For example, Skolnick et al. (Trends in Biotechnology, 2000. Vol. 18 pages 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., Abstract and Sequence-based approaches to function prediction, page 34). Even in situations where there is some

confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular Abstract and Box 2). Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only SEQ ID Nos. 245, 297, 298, and 301 meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Conclusion

14. No claims are allowed.

15. Claims 45 and 54-59 are free of the prior art. The closest prior art is Schmollinger, et al. (PNAS, 2003. Vol. 100, pages 3398-3403, as cited on the IDS). Schmollinger, et al. teach peptides JS34 (SLGSPVLGL) and JS90 (RLASFYDWPL) of the protein ML-IAP that induce an immune response and tumor cell death after vaccination of an individual with the peptides (see figures 2 and 3). Schmollinger, et al. do not teach nor reasonably suggest stimulation of a specific T-cell response with the peptides of SEQ ID Nos. 245, 297, 298 or 301.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571) 272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a

USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

July 10, 2007

LARRY R. HELMS, PH.D.
SUPERVISORY PATENT EXAMINER